REMARKS

Claims 1 to 30 are pending in the application. Claims 27 to 29 are rejected. Applicants gratefully acknowledge allowance of claims 1 to 26 and 30.

Rejection under U.S.C. § 112, First Paragraph (Written Description)

Claims 27 to 29 are rejected for allegedly failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse the rejection.

It is alleged in the Office Action that the specification does not describe the nexus between the modulation of serotonin uptake combined with $5HT_{1A}$ antagonism, and the treatment of certain medical conditions. The Office Action incorrectly suggests that modulation of the receptors germane to the instant invention involves simultaneous antagonism and agonism of the same receptor. The disclosed examples of the present invention demonstrate the characteristics of high affinity for serotonin transporters (*see* specification, ¶ 61), exemplifying the behavior of a selective serotonin reuptake inhibitor, and high affinity for serotonin $5HT_{1A}$ receptors, *i.e.*, antagonist activity at $5HT_{1A}$ receptors. The serotonin transporter (SERT) and the $5HT_{1A}$ receptor are different receptors.

Selective serotonin reuptake inhibition and $5HT_{1A}$ antagonism are not mutually hostile, and this remains the case when compounds separately functioning as an SSRI and as a $5HT_{1A}$ antagonist are mixed, as demonstrated by Blier and Bergeron, 1995; F. Artigas *et al.*, 1996; and M.B. Tome, *et al.*, 1997. Quite oppositely, in fact, swifter onset of antidepressant efficacy is observed. *See id.* This is because while the SSRI activity effects increased amounts of synaptic serotonin, which in turn is effective in alleviating various disorders, contemporaneous $5HT_{1A}$ activity blocks presynaptic serotonin receptors and prevents feedback inhibition from delaying the serotonin increase. The result is a decrease in the SSRI

latency period that otherwise leads many patients, eager for quick results, to believe that their medicinal treatment has been unsuccessful. This effect, the decrease in the SSRI latency period, clearly provides the nexus between contemporaneous modulation of serotonin uptake and $5HT_{1A}$ antagonism on the one hand, and treatment of medical conditions on the other, and refutes the notion that the modulations of serotonin uptake and $5HT_{1A}$ antagonism constitute opposite reactions with regard to the same receptor, a fact easily recognizable by a person skilled in the art.

Accordingly, the rejection of claims 27 to 29 under 35 U.S.C. § 112, first paragraph, for lacking adequate written description is inapposite, and applicants respectfully request the rejection be withdrawn.

Rejection under U.S.C. § 112, First Paragraph (Enablement)

Claims 27 to 29 are rejected for allegedly failing to comply with the enablement requirement under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse the rejection.

Applicants have already demonstrated above that persons skilled in the art recognize the nexus between treatment of medical conditions and the contemporaneous mediation of serotonin uptake and $5HT_{1A}$ antagonism.

The present Office Action incorrectly asserts that there is no testing in the present application for the inhibition of serotonin uptake. Fluoxetine, a widely-used inhibitor of 5HT uptake into serotonergic neurons, displays a binding affinity to the 5HT serotonin transporter of 1.96 nM. Applicants' testing yielded values ranging from 0.33 and 19.0 nM for the various embodiments of the claimed compound. As disclosed in the specification (page 29, ¶ 61) the binding affinity of the compounds representing the instant invention for the serotonin transporter was conclusively determined through ^{3}H-paroxetine displacement. Cheetham, *et*

al., *Neuropharmacol.*, 32(8), 737-743 (1993) establishes that there is a strong correlation between such ^{3}H-paroxetine displacement and ^{3}H-serotonin uptake inhibition. Accordingly, the protocol observed by Applicants constituted reliable testing for ^{3}H-serotonin uptake inhibition.

It is a fact well known to those skilled in the art that selective serotonin reuptake inhibition and enhancements thereof (*e.g.*, via $5HT_{1A}$ antagonism), when effected through therapeutic administration of pharmacological agents, can benefit the medical conditions described in claims 27 to 29. For example, compounds like fluoxetine (*e.g.*, Prozac®), paroxetine (*e.g.*, Paxil®), and escitalopram (*e.g.*, Lexapro®) are widely used and FDA approved to treat depression; paroxetine (*e.g.*, Paxil®) as well as fluoxetine (*e.g.*, Prozac®) have been proven efficacious and are FDA approved for treatment of panic disorder (*see* Paxil CR® Prescribing Information, page 6; Prozac® package insert, page 8; attached); sertraline and other SSRIs have been shown to have a broad range of efficacy in treatment of post-traumatic stress disorder (PTSD) and also alcoholism (*see* Brady KT, Sonne SC, Roberts JM. *Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence. J Clin Psychiatry* 1995; 56:502-5; attached); paroxetine (*e.g.*, Paxil®) has also been proven efficacious and is FDA approved for treatment of social anxiety disorder (*see* Paxil CR® Prescribing Information, page 6; attached); fluoxetine has been demonstrated an effective treatment for attention deficit/hyperactivity disorder (*see* Young LR *et al., A therapeutic class evaluation of selective serotonin reuptake inhibitors*, by Tennessee Drug Utilization Review Program, U. of Tenn., Memphis, October 13, 1998; attached); escitalopram oxalate (*e.g.*, Lexapro®) has been proven efficacious and is FDA approved for treatment of generalized anxiety disorder (GAD) (*see* Lexapro® package insert, page 3; attached); fluoxetine (*e.g.*, Prozac®) is also indicated for treatment of obsessive compulsive disorder (*see* Prozac® package insert, page 7, attached); Boyer WF. *Potential indications for the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol* 1992 Jun; 6 Suppl 5:5-12 (attached) demonstrates that the common SSRI side effect of decreased appetite and subsequent weight loss appears to be most pronounced in obese patients and may be a useful effect as an adjunct

to diet and exercise in cases of severe obesity; Boyer also reports that fluoxetine is an effective treatment for anorexia nervosa, an eating disorder, as well as premenstrual dysphoric disorder; fluoxetine (*e.g.,* Prozac®) is also indicated for treatment of bulimia nervosa, another eating disorder (*see* Prozac® package insert, page 8, attached); venlafaxine (*e.g.,* Effexor®), paroxetine (*e.g.,* Paxil®), sertraline (*e.g.,* Zoloft®), and fluoxetine (*e.g.,* Prozac®) have all been shown effective in treatment of vasomotor flushing (*see, e.g.*, Stearns V, Beebe KL, Iyengar M, Dube E. *Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA.* 2003 Jun 4;289(21):2827-34; *see also* Loprinzi CL *et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet.* 2000 Dec 16;356(9247):2059-63; both attached); fluoxetine has furthermore been demonstrated efficacious in treatment of alcoholism (*see* Janiri L, Gobbi G, Mannelli, *et al.* (1996). *Effects of fluoxetine at antidepressant doses on short-term outcome of detoxified alcoholics. Int Clin Psychopharmacol* 11:109-17; attached); and, paroxetine and other SSRIs have been used to effectively treat certain forms of sexual dysfunction (*see* Waldinger MD, Olivier B. *Utility of selective serotonin reuptake inhibitors in premature ejaculation. Curr Opin Investig Drugs.* 2004 Jul;5(7):743-7; attached). It is also well-documented that reduction of negative feedback and augmentation of the serotonin reuptake mechanism can be effected by coadministration of $5HT_{1A}$ antagonists. *See* Perez *et al.*. (cited in application at page 2, ¶ 8); *see also* Perez V, Puigdemont D, Gilaberte I, Alvarez E, Artigas F. *Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors. J Clin Psychopharmacol.* (2001) Feb;21(1):36-45; attached.

A patent need not teach, and preferably omits, what is well known in the art. See Manual of Patent Examining Procedure § 2164.01; see also *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). Thus, it would be unnecessary and superfluous to disclose with specificity which medical conditions may be treated with which embodiments when the disclosed embodiments have been shown to provide the physiological effects of serotonin reuptake inhibition and $5HT_{1A}$ antagonism, and where one skilled in the art would accept the disclosed

model as reasonably correlating to the claimed effects. See *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (reversing the decision that *in vitro* data did not support *in vivo* applications). The Office Action overstates the unpredictability in the art with regards to the correlation between serotonin reuptake inhibition/$5HT_{1A}$ antagonism and treatment of medical conditions.

Applicants respectfully submit that the specification therefore provides sufficient support for the use of the compounds of claim 1 for the treatment of the conditions described in the specification (page 31, ¶ 64) and as included in claims 27 to 29; accordingly, Applicants respectfully submit that rejection of claims 27 to 29 be withdrawn.

Conclusions

In view of the foregoing, applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at 215-568-3100.

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